We claim:

1. A DNA construct encoding a chimeric protein comprising (a) at least one receptor domain, capable of binding to a selected ligand, fused to (b) a heterologous additional protein domain capable of initiating a biological process upon exposure to the ligand, said ligand being capable of binding to two or more chimeric protein molecules.

2. A DNA construct of claim 1 wherein the chimeric protein further comprises an intracellular targeting domain capable of directing the chimeric protein to a desired cellular compartment.

3. A DNA construct of claim 2 wherein the intracellular targeting domain comprises a secretory leader sequence, a membrane spanning domain, a membrane binding domain or a sequence directing the protein to associate with vesicles or with the nucleus.

4. A DNA construct of claim 1 wherein the chimeric protein has a K_d value for binding to the selected ligand of less than or equal to about 10^{-6} M.

5. A DNA construct of claim 1 wherein the selected ligand is less than about 5 kDa in molecular weight.

6. A DNA construct of claim 1 wherein the heterologous additional protein domain comprises:

(a) a protein domain capable, upon exposure to the ligand, of initiating a detectable intracellular signal;

(b) a DNA-binding protein; or

(c) a transcriptional activation domain.

7. A DNA construct of claim 6 wherein the intracellular signal is capable of activating transcription of a gene under the transcriptional control of transcriptional control element responsive to said oligomerization.

8. A DNA construct of claim 7 wherein the additional protein domain is the zeta subunit of CD3.

9. A DNA construct of any of claims 1-8 wherein the chimeric protein is capable of binding to an FK506-type ligand, a cyclosporin A-type ligand, tetracycline or a steroid ligand.

10. A DNA construct encoding a target gene under the transcriptional control of an transcription control element responsive to the oligomerization of a chimeric protein of any of claims 1-9.

11. A DNA construct of claim 10 in which the target gene is not naturally under the transcriptional control of the responsive transcriptional control element.

12. A DNA construct containing (a) a transcriptional control element responsive to the oligomerization of a chimeric protein of claims 1-9 and (b) flanking DNA sequence from a target gene permitting the homologous recombination of the transcriptional control element into a host cell in association with the target gene.

13. A DNA construct of claims 10 - 12 wherein the target gene encodes a surface membrane protein, a secreted protein, a cytoplasmic protein or a ribozyme or an antisense sequence.

SUB a'

14. A DNA vector containing a DNA construct of any of claims 1-13 and a selectable marker permitting transfection of the DNA construct into host cells and selection of transfectants containing the construct.

15. A DNA vector of claim 14 wherein the vector is a viral vector.

16. A viral vector of claim 15 which is an adeno-, adeno associated- or retroviral vector.

SUB a2

17. A chimeric protein encoded by a DNA construct of any of claims 1-9.

18. A cell containing and capable of expressing at least one DNA construct of any of claims 1-13.

~~19. A cell of claim 18 which is a mammalian cell.~~

20. A cell of claim 18 which contains

(a) a first DNA construct encoding a chimeric protein comprising (i) at least one receptor domain capable of binding to a selected ligand and (ii) another protein domain, heterologous with respect to the receptor domain, but capable, upon oligomerization with one or more other like domains, of triggering the activation of transcription of a target gene under the transcriptional control of a transcriptional control element responsive to said oligomerization; and

(b) a target gene under the expresssion control of a transcriptional control element responsive to said oligomerization;

and which following exposure to the selected ligand expresses the target gene.

21. A cell of claim 18 which contains a first set of DNA constructs encoding

(a) a first chimeric protein containing a DNA-binding domain and at least one receptor domain capable of binding to a first selected ligand moiety; and

(b) a second chimeric protein containing a transcriptional activating domain and at least one receptor domain capable of binding to a second selected ligand (which may be the same or different from the first selected ligand moiety); and

and a second DNA construct encoding a target gene under the transcriptional control of a heterologous transcriptional control sequence which binds with the DNA-binding domain and is responsive to the transcriptional activating domain;

which cell expresses the target gene following exposure to a substance containing the selected ligand moiety(ies).

Sub B5

22. A DNA composition comprising

(a) a first DNA construct encoding a chimeric protein comprising (i) at least one receptor domain, capable of binding to a selected ligand, fused to (ii) a heterologous additional protein domain capable of initiating a biological process upon exposure to the ligand; and

(b) a second DNA construct encoding a target gene under the transcriptional control of an transcription control element responsive to the oligomerization of a chimeric protein.

23. A DNA composition comprising

(a) a DNA construct encoding a first chimeric protein comprising (i) at least one first receptor domain, capable of binding to a selected first ligand moiety, fused to (ii) a heterologous additional protein domain capable of initiating a biological process upon exposure to the ligand in the presence of a second chimeric protein; and,

(b) a DNA construct encoding the second chimeric protein comprising (i) at least one receptor domain, capable of binding to a selected second ligand moiety, fused to (ii) a heterologous additional protein domain capable of initiating a biological process upon exposure to the ligand in the presence of the first chimeric protein;

wherein the first and second receptor moieties may be the same or different and the first and second selected ligand moieties may be the same or different; and

(c) a target DNA construct encoding a target gene under the transcriptional control of a transcriptional control element responsive to the oligomerization of a chimeric protein.

Sub A3 Cont'd.

24. A ligand capable of binding to two or more chimeric protein molecules of claims 1-9 to form an oligomer thereof, said ligand having the formula:

Sub q3 concl'd.

linker—{rbm$_1$, rbm$_2$, ...rbm$_n$}

wherein n is an integer from 2 to about 5, rbm(1)-rbm(n) are receptor binding moieties which may be the same or different and which are capable of binding to the chimeric protein(s), said rbm moieties being covalently attached to a linker moiety which is a bi- or multi-functional molecule capable of being covalently linked ("—") to two or more rbm moieties.

25. A ligand of claim 24 which has a molecular weight less than about 5 kDa.

26. A ligand of claim 24 wherein the rbm moieties are the same or different and comprise an FK506-type moiety, a cyclosporin-type moiety, a steroid or tetracycline.

27. A ligand of claim 24 which binds to a naturally occurring receptor with a Kd value greater than about 10^{-5}.

28. A ligand of claim 24 wherein at least one rbm comprises a molecule of FK506, FK520, rapamycin or a derivative thereof modified at C9, C10 or both.

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29 28. A ligand of claim 24 wherein the linker moiety comprises a C2-C20 alkylene, C4-C18 azalkylene, C6-C24 N-alkylene azalkylene, C6-C18 arylene, C8-C24 ardialkylene or C8-C36 bis-carboxamido alkylene moiety.

30 29. The use of a ligand of claim 24 to prepare a pharmaceutical composition for activating the transcription of a target gene.

31 30. A method for activating the transcription of a target gene in cells which comprises

(a) providing cells containing and capable of expressing (i) at least one DNA construct of claim 7 and (ii) a target gene under the expression control of a transcription control element responsive to the oligomerization of said DNA construct; and,

(b) exposing the cells to a ligand capable of binding to the chimeric protein encoded by the DNA construct in an amount effective to result in expression of the target gene.

32
31. A method of claim 30 wherein the cells are grown in a culture medium and the exposing is effected by adding the ligand to the culture medium.

33
32. A method of claim 30 wherein the cells are present within a host organism and the exposing is effected by administering the ligand to the host organism.

34
33. A method of claim 32 wherein the host organism is a mammal and the ligand is administered by oral, bucal, sublingual, transdermal, subcutaneous, intramuscular, intravenous, intra-joint or inhalation administration in an appropriate vehicle therfor.

35
34. A method for providing a mammal responsive to a ligand of claim 24 which comprises introducing a cell of claim 18 into a host mammal.

36
35. A method for providing a mammal responsive to a ligand of claim 14 which comprises introducing at least one vector of claim 14 into a host mammal under conditions permitting transfection of one or more cells of the host mammal.

37
36. A kit which comprises at least one DNA construct ~~of any~~ of claims 1-~~9~~.

38
37. A kit of claim 36 which further comprises a ligand to which one or more of the chimeric proteins encoded by the DNA construct(s) bind.

39
38. A kit of claim 37 which further comprises a monomeric ligand reagent as an antagonist for ligand-chimeric protein binding.

40
39. A kit of claim 36 which further comprises at least one DNA construct of claims 10 - 13.

41
40. A kit containing a first DNA construct encoding a chimeric protein containing at least one receptor domain (capable of binding to a selected

ligand), fused to a transcriptional activator domain; a second DNA construct encoding a second chimeric protein containing at least one one receptor domain (capable of binding to a selected ligand), fused to a DNA binding domain; and a third DNA construct encoding a target gene under the control of a transcriptional control element containing a DNA sequence to which the DNA binding domain binds and which is transcriptionally activated by exposure to the ligand in the presence of the first and second chimeric proteins.

42
~~40~~. A kit of any of claims 36 - 38 in which each DNA construct is linked to a selection marker, which may be the same or diffferent for each different DNA construct, permitting the selection of cells which contain said DNA construct(s).

43
~~41~~. A kit of any of claims 36-38 in which one or more of the DNA constructs contains a cloning site in place of an action domain or target gene.

44
~~42~~. A kit of claim 39 which further comprises positive control cells stably transformed with the DNA construct(s) which are provided in the kit.

45
~~43~~. A host organism containing a cell of claim 18.

46
~~44~~. A host organism of claim 43 which is a plant or animal organism.

47
~~45~~. An animal of claim 44 which is a worm, insect or mammal.

48
~~46~~. A mammal of claim 45 which is a mouse or other rodent or a human.